PATENT
1110-0306P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	Hidemitsu NISHIDA et al.	Conf.:	9102
Appl. No.:	10/026,606	Group:	1624
Filed:	December 27, 2001	Examiner:	S. Patel
For:	TRICYCLIC COMPOUND HAVING SPIRO UNION		

PETITION UNDER 37 C.F.R. §1.144

Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

August 17, 2004

Sir:

Applicants respectfully petition for rejoinder of Groups I and II.

In the Restriction Requirement of November 20, 2003, the Examiner restricted the claims into the following two (2) groups.

Group I, claims 19-29, in part, wherein X is nitrogen; Y is oxygen, NH or imino; m is 0; n is 1, thus forming compounds having 3-fused rings; and

Group II, claims 19-29, in part, drawn to compounds not included in Group 1, wherein X is CH; Y is O, NH, S, SO or SO_2; and m and n form compounds having a 7-membered ring fused with a 6-membered ring or when n is 2 or 3, to form a compound having a 7-

or 8-membered ring, which is fused with a 5-, 6- or 7-membered heterocycle having a Y variable.

The Examiner additionally required an election of species.

On December 22, 2003, Applicants timely elected, with traverse, Group I. In response to the election of species Applicants elected the compound of Example 1.

Applicants, respectfully petition that the restriction of Groups I and II be withdrawn and the subject matter of these groups (claims 19-29 in their entirety) be rejoined.

The different substituents restricted by the Examiner into separate groups are recited as Markush groups. The restriction of elements recited in Markush groups is governed by M.P.E.P. §803.02, which states, "it is improper for the Office to refuse to examine that which applicants regard as their invention unless the subject matter in a claim lacks unity of invention of invention. *In re Harnisch*, 206 USPQ 300 (CCPA 1980)...unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." Both a common utility and a substantial structural feature are present with Groups I and II, so the restriction is entirely without basis.

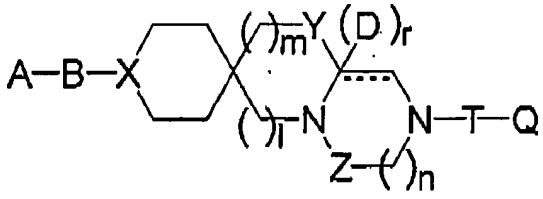
Both the MPEP and case law support Applicants' position that the Examiner's requirement for restriction regarding Groups I and II in this matter is not correct. A short discussion of Harnisch is useful given the MPEP's reliance on this case. Claim 1 of Harnisch was directed to courmarin compounds. The Examiner in Harnisch rejected the claims under 35 U.S.C. §121 "as containing an improper Markush group and misjoinder." The Examiner in the present application is using virtually the same reasoning as in Harnisch in support of the restriction requirement, that is, "the instant generic claim constitutes an improper joinder of inventions." See, for example, Paragraphs 5 and 6 on pages 4 and 5, of the Office Action. The common utility and shared substantial structural feature, which is essential to the utility of the invention are discussed below.

(1) Common utility -

The present invention is based on the discovery by the inventors that compounds of Formula (I) with a tricyclic core with a spiro union have the common utility of inhibiting activated blood coagulation factor X (FXa) and therefore acting as anticoagulants. See page 1, second paragraph of the specification.

(2) Shared substantial structural feature disclosed as being essential to the common utility -

The compounds of Groups I and II share the common structural feature of a tricyclic compounds having a spiro skeleton. See Formula (I) below.



(I)

The present invention is based on the discovery that the compounds of formula (I) having the indicated spiro skeleton have extremely potent FXa inhibitory activity, as described on page 11 lines 3 to 9 of the specification. The compounds of the invention have a novel tricyclic structure having a spiro union, e.g., 1,4-diaza-7-oxa-1'-spiro[bicyclo [4.3.0] nonane-8, 4'-piperidin] ring, 1,4,7-triaza-spiro [bicyclo [4.3.0] nonane-8, 4' -piperidin] ring or the like.

The novel structure of the invention is very important. As discussed in the Examples describing the X-ray crystallography analysis, found on line 15 of page 350 through line 9 of page 358 in the specification and from line 23 of page 357 to line 9 of page 358, the tricyclic compounds of the invention, including the novel

spiro union, contributed to having been able to find the novel pharmacophore of the invention, which had not been reported for already-known Fxa inhibiting compounds, by fixing the tricyclic three-dimensional conformation to specific coordinate positions.

As discussed on page 9, lines 1-17 of the specification, the present invention determined, for the first time, what kind of structure should be studied for developing different types of FXa inhibitors. In addition, as a result of the present work, the demerits of already-known FXa inhibitors such as DX-9065a and FX-2212a, whose availability with oral administration is insufficient and which have side effects from amidino groups or guanidine groups, were overcome. The information obtained from the present work regarding the interactions between FXa and FXa-inhibitory compounds based on the data of the crystal structure of the complex between the FXa and the FXa-inhibitory compounds of the invention is ground-breaking and extremely important in the field of FXa inhibitors.

The Examiner asserts that the substituents in the generic formula (I) of Group I (e.g. X, Y, m, l and n) should be limited as discussed on page 2, Item 3 of the Restriction Requirement of November 20, 2003, a copy of which is attached hereto. Specifically, the Examiner asserts that the working examples only

disclose 6:5:6 rings and that other combinations, such as 6:6:6, 6:7:6 or 6:7:7 tricyclic heterocycles are not supported by the specification.

However, the Examiner is mistaken in this position. Attention is directed to Example 8 of the specification, which discloses a tricyclic heterocycle that is a 6:6:6 combination and has the spiro frame structure of 2,4-diaza-7-oxa-spirobicyclo [4.4.0]decane-2-one. Thus, the specification discloses other than 6:5:6 combinations. This compound is described on page 207, line 17 to page 212, line 16, including the detailed description of the synthesis of the compound. As discussed in the specification, the compound of Example 8 can be synthesized using the general production methods of the invention that are described on page 93, line 23 to page 144, line 6 of the specification. Other ring combinations are similarly sufficiently disclosed from the general production methods, which include various ring combinations. As such, Applicants believe that the invention should not be limited as suggested by the Examiner.

In addition, the Applicants have tested several additional compounds having various sizes of spiro rings and heteroatoms that are encompassed by formula (I). The structures of the Compounds (1) to (7) are shown on "Attachment A". The Compounds (1) to (7)

were synthesized using the methods described in the specification. The compounds (1) to (7) are also shown in the Table 1, below, wherein it is shown that the compounds have an inhibitory activity within the range recited in the specification on page 165, lines 3-6.

TABLE 1

Compound	Ring Combination	Y	M	l	n	IC50(nm)*
1	6:5:6	S	0	1	1	1.3
2	6:5:6	SO_2	0	1	1	2.3
3	6:6:6	NH	1	1	1	3.5
4	6:6:6	S	1	1	1	25
5	6:5:7	NH	0	1	2	11
6	6:6:7	NH	1	1	2	884
7	6:5:7	O	1	0	2	96

*Fxa inhibitory action was measured in accordance with the test method described on page 164 of the specification.

As noted above, not only 6:5:6 ring combinations, but various other ring combinations can also be produced using the methods described in the specification. In addition, compounds may be made wherein Y is S or SO_2, or wherein m is 0 or 1; l is 0 or 1; and n is 1 or 2. The Fxa inhibitory action with the above-compounds is within the range of the inhibitory action described in the specification on page 165, lines 3-6.

The data of Table 1 evidences that compounds exemplifying the full scope of Formula (I) can be synthesized using the methods described in the specification and such compounds have inhibitory

activity for Fxa as described in the specification. Accordingly, Applicants assert that specification as originally filed contains sufficient support for the scope of the claimed invention and it is not necessary to further limit the definitions recited for formula (I).

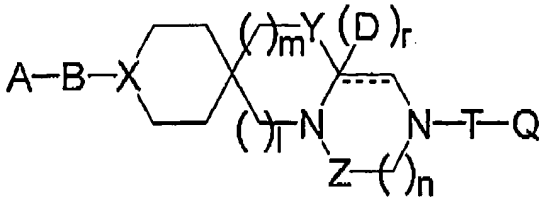
Finally, Applicants note that the Examiner indicates in the Office Action of March 17, 2004, that a search of the compounds in Group I results in more than 4000 total hits. However, if the invention is structure searched using the CAS:STN Registry, which is commonly used to in the field of chemistry, there are only 599 compounds/hits total. In addition, all of the compounds are embodied in either WO/02/05368 (corresponding to U.S. App. No. 10/451,728) or the present application, which has the same assignee as the '728 application.

The REGISTRY File is a chemical structure and dictionary database containing substance records for substances identified by the CAS (Chemical Abstracts Service) Registry System. The database includes substances indexed in Caplus, CA and CAOLD files, as well as special registrations for, for example, regulatory lists such as TSCA and EINECS.

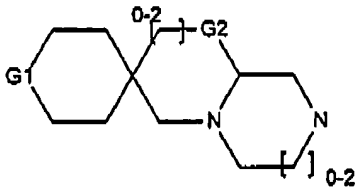
When the present invention is search using the following partial structure search with the REGISTRY File, as indicated above

only 599 compounds are identified, which fall in only two references.

Formula (I)



(I) m=0,1,2 n=0,1,2 l=1
X=C,N Y=N,O,S



G1=C,N
G2=O,S,N,C

Applicants note that "l" was fixed as 1 for search. Using this standard search strategy, it is possible to search the skeletons having ring sizes of 6-5-5, 6-5-6, 6-5-7, 6-6-5, 6-6-6, 6-6-7, 6-7-5, 6-7-6, 6-7-7 as one search with one search formula. It is easily recognizable from this search that the compounds of formula (I) have unique spiro skeleton.

Thus, the compounds of Groups I and II share a common structural feature of the tricyclic core having a spiro union and this spiro skeleton has been shown to be essential for the common utility of FXa inhibitory activity. As such, Applicants respectfully petition for rejoinder of the claims of Groups I and II.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong (Reg. No. 40,069) at the telephone number of the undersigned below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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GMM/MAA/

Attachments: Restriction Requirement of November 20, 2003